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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 95.82307/002	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/GB2004/004696	International filing date *(day/month/year)* 05.11.2004	Priority date *(day/month/year)* 07.11.2003
International Patent Classification (IPC) or national classification and IPC A61K9/127, A61K38/00, A61K38/11, A61K38/23, A61K38/31		
Applicant CAMURUS AB et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 3 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
07.09.2005	09.12.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Pacreu Largo, M Telephone No. +49 89 2399-7851

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/004696

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-36 as originally filed

   Claims, Numbers

   1-21 received on 11.10.2005 with letter of 06.10.2005

   Drawings, Sheets

   1/3-3/3 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☒ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☒ the claims, Nos. 1-23 as originally filed
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 20,21

because:

☒ the said international application, or the said claims Nos. 20,21 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/004696

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-21
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-21
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-19
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 20 and 21 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. The documents cited in the International Search Report are consecutively numbered D1-D9 in the order of their listing. If not indicated otherwise, reference is made to the passages cited in said ISR.

2. The subject-matter of claims 1-21 appears to be novel in the sense of Art. 33(2) PCT since compositions according to present claim 1 are not disclosed in any of the documents of the search report.

3. The subject-matter of claim 1-21 also involves an inventive step, Article 33(3) PCT, for the following reasons:

   Non-lamellar liquid crystalline phases are well known as delivery systems for drugs, e.g. peptides. These systems prolongs the half-life of peptides (peptides are protected from enzymatic degradation) and allow a sustained release (see e.g. D1, D2, p.261, D4, D6). Most of the systems comprise polar lipids, preferably monoolein, and form liquid crystalline phases in contact with aqueous media.

   The problem to be solved by the present application appears to be the provision of an improved non-lamellar liquid crystalline delivery system for cationic peptides for oral administration, as well as a depot formulation for intramuscular or subcutaneous injection.

The solution suggested is the addition of an anionic lipid, particularly a fatty acid, which increases the lifetime of cationic peptides upon oral, subcutaneous or intramuscular administration.

The applicant has provided *in vivo* studies with rats showing that the bioavailability of calcitonin formulations incorporating oleic acid is higher than without oleic acid in both oral and subcutaneous formulations (see examples 4, 6; figures 2, 3).

4. For the assessment of the present claims 20 and 21 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI

Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO2004080438	23.09.2004	12.03.04	14.03.03

CLAIMS:

1) A composition comprising at least one cationic peptide active agent having an isoelectric point of above 7.0, at least one neutral structure forming amphiphile, 0.5 to 20% of at least one anionic structure forming amphiphile and optionally at least one solvent, wherein the non-polar groups of the structure forming amphiphiles are selected from C_6-C_{32} alkyl and alkenyl groups characterised in that said composition comprises a non-lamellar phase structure and/or forms a non-lamellar phase structure on exposure to body fluids.

2) A composition as claimed in claim 1 wherein said non-lamellar phase is a cubic, hexagonal phase or L_3 phase.

3) A composition as claimed in claim 1 or claim 2 wherein said cationic peptide is a peptide hormone.

4) A composition as claimed in any of claims 1 to 3 wherein said cationic peptide is selected from the group consisting of desmopressin, octreotide, salmon calcitonin and human calcitonin.

5) A composition as claimed in any of claims 1 to 4 wherein the oral bioavailability is at least 1% when measured as blood plasma concentration of active agent relative to intravenous administration in slaine solution.

6) A composition as claimed in any of claims 1 to 5 further comprising a peptidase inhibitor.

7) A composition as claimed in any of claims 1 to 6 wherein said neutral structure forming amphiphile comprises at least one of glyceryl monooleate, glyceryl monolinoleate, glyceryl dioleate (GDO), dioleyl phosphatidyl ethanolamine (DOPE), dioleyl phosphatidylcholine (DOPC) and phytantriol, lyso-oleyl phosphatidylcholine (LOPC) and mixtures thereof.

8) A composition as claimed in any of claims 1 to 7 wherein said anionic structure forming amphiphile comprises at least one fatty acid.

9) A composition as claimed in claim 8 wherein said fatty acid is at least one of

caproic, caprylic, capric, lauric, myristic, palmitic, phytanic, palmitolic, stearic, oleic, elaidic, linoleic, linolenic, arachidonic, behenic or lignoceric acids, their salts or mixtures thereof.

10) A composition as claimed in any of claims 1 to 9 wherein said anionic structure forming amphiphile is present in a quantity sufficient to increase the half-life of said peptide active agent in a solution of carboxypeptidase C by at least 50% relative to the half-life of an equivalent composition not including said anionic structure forming amphiphile.

11) A composition as claimed in any of claims 1 to 10 further comprising a fragmentation agent.

12) A pharmaceutical formulation comprising a composition as claimed in any of claims 1 to 11 and at least one pharmaceutically tollerable carrier or excipient.

13) A composition as claimed in any of claims 1 to 4 which comprises or forms particles of said non-lamellar phase structure.

14) A composition as claimed in claim 13 wherein said particles are colloidal.

15) A composition as claimed in any of claims 1 to 12 further comprising an oxygen containing biotollerable organic solvent.

16) A composition as claimed in claim 15 in the form of a solution which forms a bulk non-lamellar phase upon contact with a body fluid.

17) A composition as claimed in claim 16 wherein said composition comprises a diacyl glycerol.

18) A composition as claimed in any of claims 15 to 17 wherein said active agent is released over a period of at least 2 to 14 days.

19) A method for the formation of a compositionas claimed in any of claims 1 to 14 comprising forming particles of non-lamellar phase and/or particles which generate non-lamellar phase on exposure to body fluids, said particles comprising at least one neutral structure forming amphiphile, at least one anionic structure

forming amphiphile or salt thereof and optionally at least one solvent, and subsequently contacting said particles with a solution of cationic peptide active agent.

20) A method for administering a cationic peptide to a patient comprising injection of a composition as claimed in claim 15 wherein in use said composition subesquently forms a non-lamellar "depot" *in vivo*, upon contact with a body fluid.

21) A method for protecting a peptide active agent from enzymic degredation *in vivo* said method comprising formulating said active agent as a composition as claimed in any of claims 1 to 18.